Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: McKinlay CJD, Alsweiler JM, Ansell JM, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. N Engl J Med 2015;373:1507-18. DOI: 10.1056/NEJMoa1504909

Supplementary Appendix

Contents

1. CHYLD Study Group

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2. Authors' Roles

JEH, JMA, JMAn, JGC, GDG, DLH, BT, TAW, NSA and RJ designed the study; DLH, JMAn, TYY, NSA and NP assisted with data collection; GGD, YJ, CJDM and MS performed the analysis; CJDM and JEH drafted the manuscript; and The CHYLD Study Steering Group (JEH, JMA, JGC, DLH, BT, TAW) had sole responsibility for the decision to publish. CJDM takes responsibility for the integrity of the data analysis. Sponsors had no role in study design, conduct, data analysis or the decision to publish.

3. Vision assessment

Vision screening included acuity (Cardiff Acuity Cards), stereopsis (Frisby Near and Lang Stereotests), alignment and motility (including cover test, 20^{Δ} base-out prism test), and non-cycloplegic autorefraction (Suresight^{TM} Autorefractor, Welch Allyn, Skaneateles Falls, NY).[1] A vision impairment score assigned one point for each of the following: internal or external ocular health problem, strabismus, abnormal motility, absence of stereopsis, binocular visual acuity >0.5 logMAR. Blindness was defined as acuity ≥1.4 logMAR in both eyes. Children were assigned a refractiveb error score consisting of one point for each of the following: hyperopia (M ≥+4.00 dioptre [D]), myopia (M ≤-1.00 D), astigmatism (C ≤-1.50 D in any axis), and anisometropia (difference in M between eyes of ≥3.00 D in either the most positive or negative meridian).[2] Left or right eyes were selected at random for analysis.

4. **Supplementary Table S1: Characteristics of children, and their mothers, who did and did not participate in the CHYLD Two-year Study**

	Participant			Non-participant
	Total	Hypoglycemia	No hypoglycemia	
Maternal baseline characteristics	N=376	N=201	N=175	N=115
Gravity, median (IQR)	2 (1, 3)	2 (1, 4)	2 (1, 3)	2 (1, 4)
Parity, median (IQR)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)
Weight gain in pregnancy__kg	11.7 (7.0)	11.7 (7.5)	11.6 (6.4)	13.1 (7.0)
Smoking during pregnancy, n (%)	103 (28)	58 (31)	45 (27)	NA
Alcohol during pregnancy, n (%)	37 (11)	21 (11)	16 (10)	NA
Highest education level, n (%)				NA
Schooling incomplete	77 (20)	40 (20)	37 (21)	
High school (≥3 years)	68 (18)	34 (17)	34 (19)	
Tertiary, technical or trade	119 (32)	69 (34)	50 (29)	
University	112 (30)	58 (29)	54 (31)	
Neonatal characteristics	N=404	N=216	N=188	N=124
Vaginal birth, n (%)	247 (61)	129 (60)	118 (63)	82 (66)
Apgar <5 at 5 min, n (%)	0	0	0	0
Feeds in first week, n (%)		**		
Breast milk only	162 (40)	72 (33)	90 (48)	38 (31)
Formula milk only	13 (3)	5 (2)	8 (4)	5 (4)
Breast and formula milk	229 (57)	139 (65)	90 (48)	81 (65)

IQR, interquartile range; NA, not available (data collected at two-year follow-up); NICU, neonatal intensive care. Hypoglycemia defined as an episode of ≥1 consecutive blood glucose concentrations <47 mg/dl (<2.6 mmol/L). **P<0.01 for comparison between children with and without neonatal hypoglycemia. Data missing for weight gain in pregnancy (participant n=18, non-participant n=9), smoking (participant n=9), and alcohol (participant n=9). Denominators represent available data.

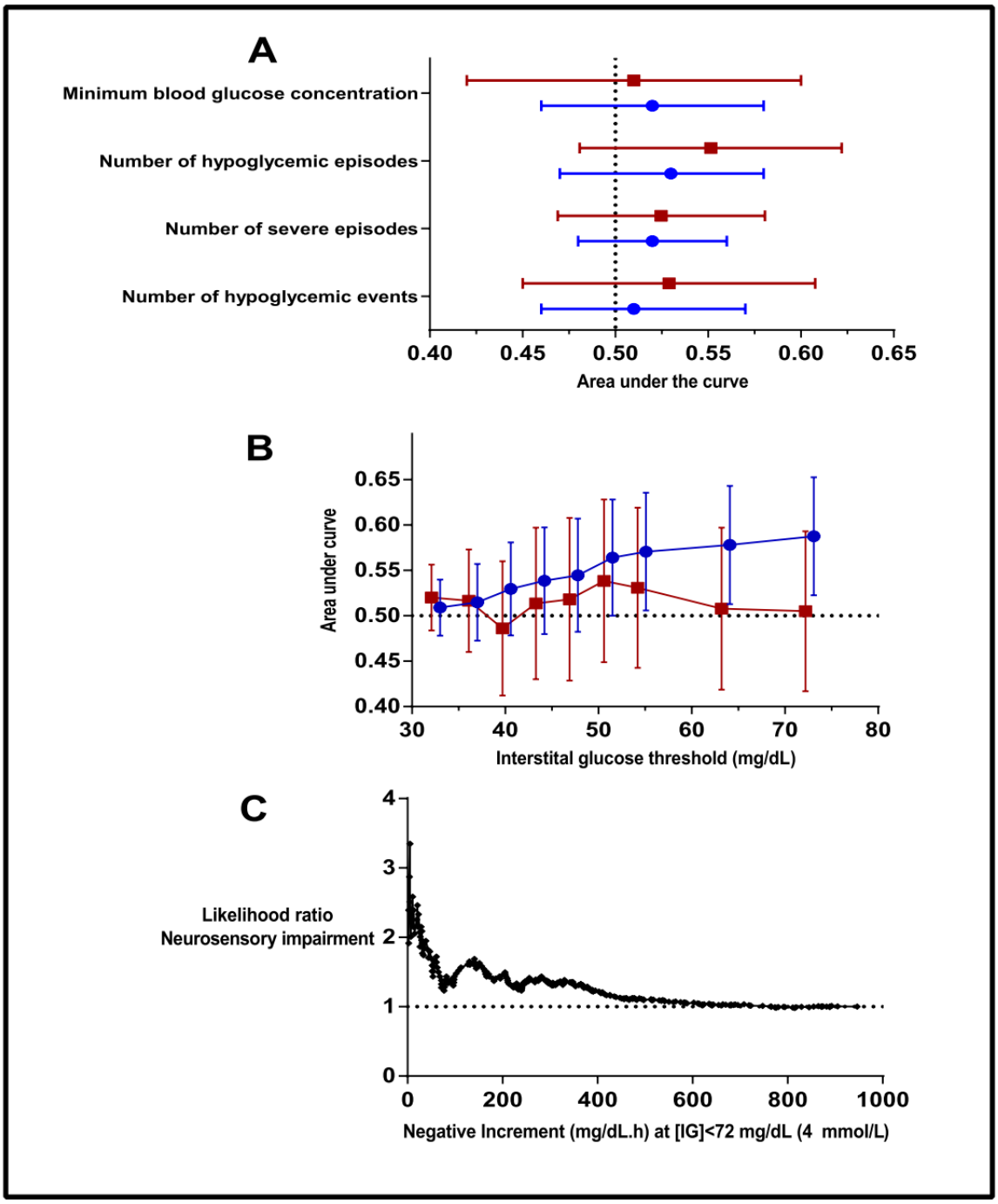
5. Supplementary Table S2: Secondary outcomes at two years in children with and without neonatal hypoglycemia

Outcome	Hypoglycemia N=216		No hypoglycemia N=188		Adjusted mean difference or risk ratio (95% CI)	P
Executive dysfunction, n (%)	13 (6)	207	16 (9)	177	0.77 (0.38, 1.57)	0.47
BRIEF-P T-score		214		184		
Inhibitory Self-Control Index	54.8 (10.3)		55.4 (10.7)		-1.1 (-3.1, 1.0)	0.31
Flexibility Index	52.6 (10.1)		52.6 (10.4)		-0.5 (-2.6, 1.5)	0.61
Emergent Metacognition Index	59.3 (11.6)		60.3 (12.6)		-1.5 (-3.9, 0.8)	0.20
Global Executive Composite	57.3 (11.0)		58.0 (12.2)		-1.4 (-3.6, 0.9)	0.23
Visual processing difficulty, n (%)	15 (7)	204	14 (8)	175	0.94 (0.46, 1.92)	0.87
Vision impairment score, n (%)		215		186	1.11 (0.76, 1.62)*	0.58
1	48 (22)		29 (16)			
2	6 (3)		10 (5)			
3	1 (1)		1 (1)			
Refractive error score, n (%)		113		93	0.64 (0.28, 1.50)*	0.31
1	8 (7)		10 (11)			
2	1 (1)		0 (0)			
3	0 (0)		1 (1)			
Cerebral palsy, n (%)	2 (1)	216	2 (1)	185	0.81 (0.11, 5.99)	0.83
Seizures (any), n (%)	10 (5)	212	11 (6)	184	0.71 (0.31, 1.64)	0.42
Hearing impairment, n (%)	3 (1)	212	2 (1)	183	1.10 (0.18, 6.60)	0.91
Blind, n (%)	0 (0)	216	0 (0)	188	-	-

Data are mean (SD) unless otherwise specified. *Count ratio. BRIEF-P, Behavior Rating Inventory of Executive Function. Hypoglycemia defined as an episode of ≥1 consecutive blood glucose concentrations <47 mg/dl (<2.6 mmol/L). Executive dysfunction defined as Executive Function Score more than 1.5 SD below cohort mean. Visual processing difficulty defined as motion coherence threshold more than 1.5 SD above cohort mean. Hearing impairment defined as need for hearing aids. See vision assessment for definition of vision impairment score and refraction error score. Denominators represent available data. Results adjusted for socioeconomic decile, sex and primary risk factor for neonatal hypoglycemia.

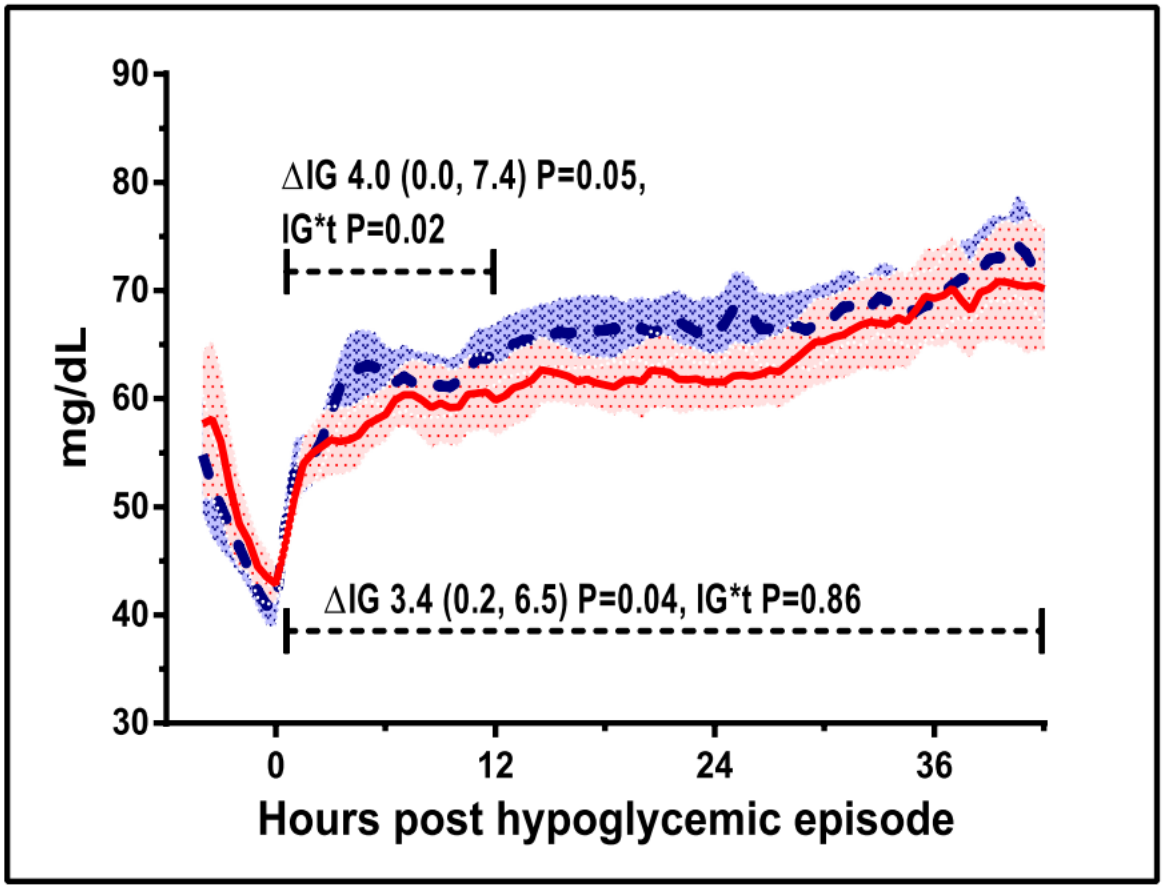
6. Supplementary Figure S1: Prediction of neurodevelopmental outcome

Supplementary Figure 1 Legend: ● Neurosensory impairment (blue circle); ■ Processing difficulty (red square). A) Area under curve (95% confidence interval) from receiver operator characteristic curves for continuous measures of hypoglycemia. Hypoglycemic episode defined as ≥1 consecutive blood glucose concentrations <47 mg/dl (<2.6 mmol/L), with severe <36 mg/dl (<2.0 mmol/L). Interstitial episode defined as ≥10 min below these thresholds. An event is either a blood or interstitial episode. B) Area under curve (95% confidence interval) from receiver operator characteristic curves for negative glucose increment at different interstitial glucose thresholds (confidence intervals that exclude 0.50 indicate P<0.05 for area > chance). C) Relationship between likelihood ratio for neurosensory impairment and negative interstitial glucose increment at < 72 mg/dL (<4 mmol/L).



7. Supplementary Figure S2: Interstitial glucose of children with neonatal hypoglycemia who did and did not receive dextrose treatment (N=162)

Supplementary Figure 2 Legend: Solid line (red), no dextrose treatment; broken line (blue), neonatal dextrose treatment. Data are mean (95% confidence interval) and represent per subject half-hour average of continuous interstitial glucose concentration (mg/dL). ΔIG, mean difference (95% confidence interval), determined from repeated measures analysis. IG*t, group-time interaction.



8. References

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